Optimizing Women's Reproductive Health

Diagnosing and Managing Vaginitis, Cervicitis and Pelvic Pain

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STD Advances Update

October 25, 2007

Honolulu, HI

CALIFORNIA STD/HIV PREVENTION TRAINING CENTER

Vaginitis

- Common etiologies
  - Bacterial Vaginosis (BV) 40 -50%
  - Vulvovaginal Candidiasis 20 -25%
  - Trichomoniasis 15 -20%

- Common vexation
  - Recurrence!!

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Complex Normal Vaginal Ecosystem

- Estrogen stimulation
  - Adequate squamous cell thickness
- Lactobacilli
  - Produce H_2O_2 and lactic acid
  - Acidic pH: <4.5
- Mucosal immunity

Factors Affecting Normal Vaginal Flora

- Douches; other feminine hygiene products
- Antibiotics and antifungal treatments
- Hormones
- Spermicides, lubricant
- Semen
- Menses

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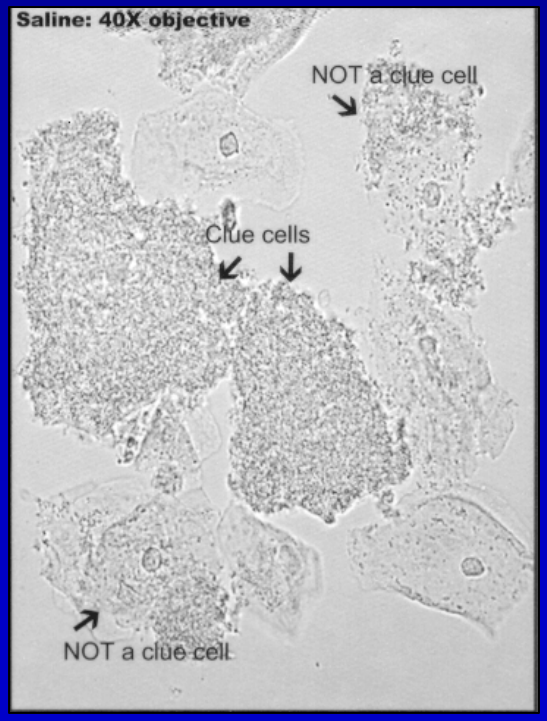
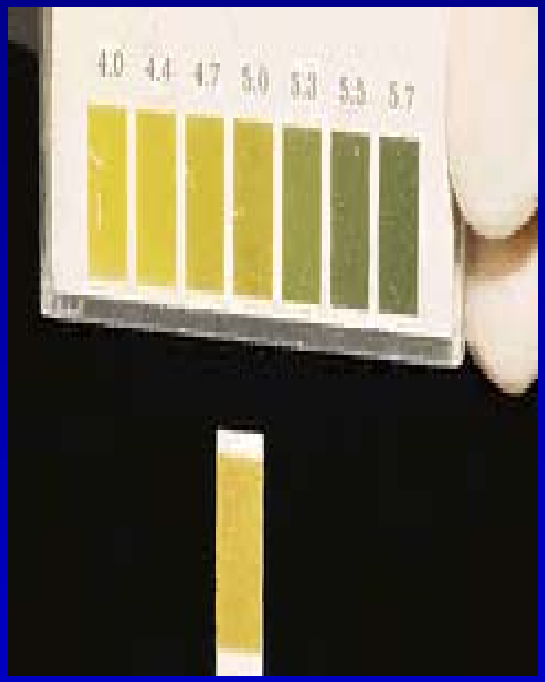
Bacterial Vaginitis

Mosby

STD Atlas, 1997



Seattle STD/HIV
Prevention Training Center



Mosby

STD Atlas, 1997

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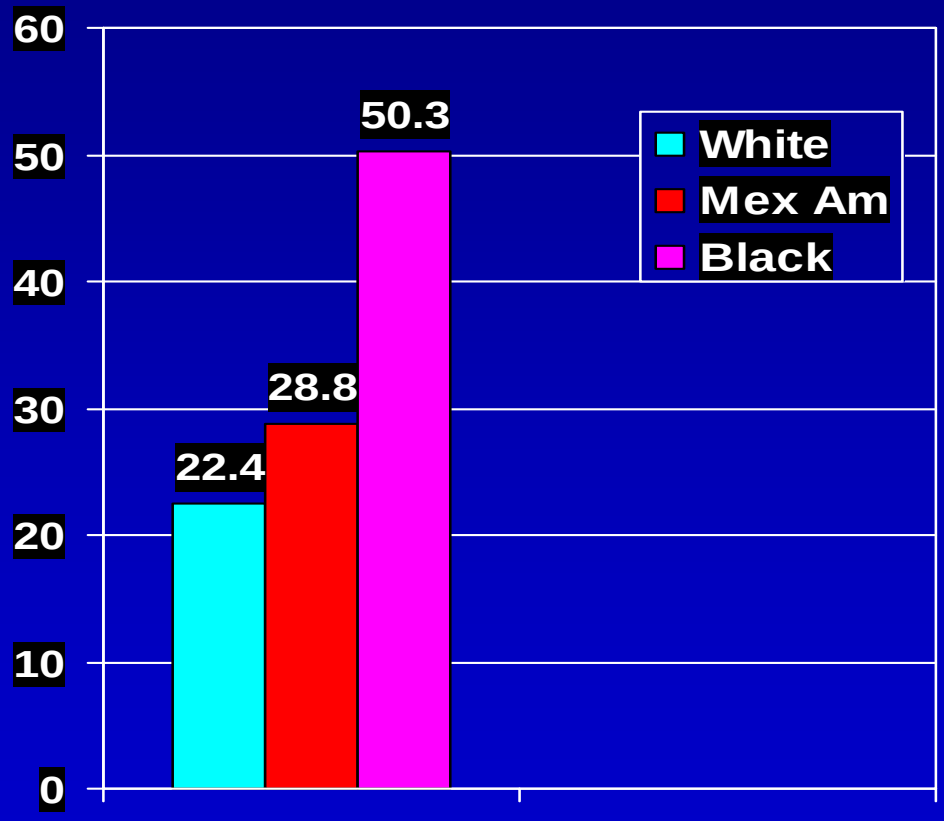
Epidemiology, BV NHANES* 2001-2002

- Overall prevalence of BV: 29%
- Only 16% reported vaginal symptoms in the past month



BV: By race/ethnicity

*National Health and Nutrition Education survey

BV: Pathology

- Disturbance of normal vaginal flora
  - ↓ Loss of H_2O_2-producing lactobacilli
  - ↑ Increase in Gram-variable coccobacilli, anaerobic organisms, genital mycoplasmas
- Production of cytokines and proteases that damage normal vaginal defenses
- Unidentified players?
  - Unrecognized pathogen(s), perhaps sexually transmitted

Polymicrobial Nature of Bacterial Vaginosis

- Vaginal samples from 27 women with BV and 46 without BV
- Bacteria identified by PCR (polymerase chain reaction) and FISH (fluorescent in situ hybridization)
- Women w/o BV: 1-6 bacterial species
- Women with BV: 9-17 bacterial species
- Thirty-five unique species identified in BV
  - Three previously undescribed BV-associated bacteria (Clostridiales)

Fredricks D et al,
NEJM, Nov 3, 2005

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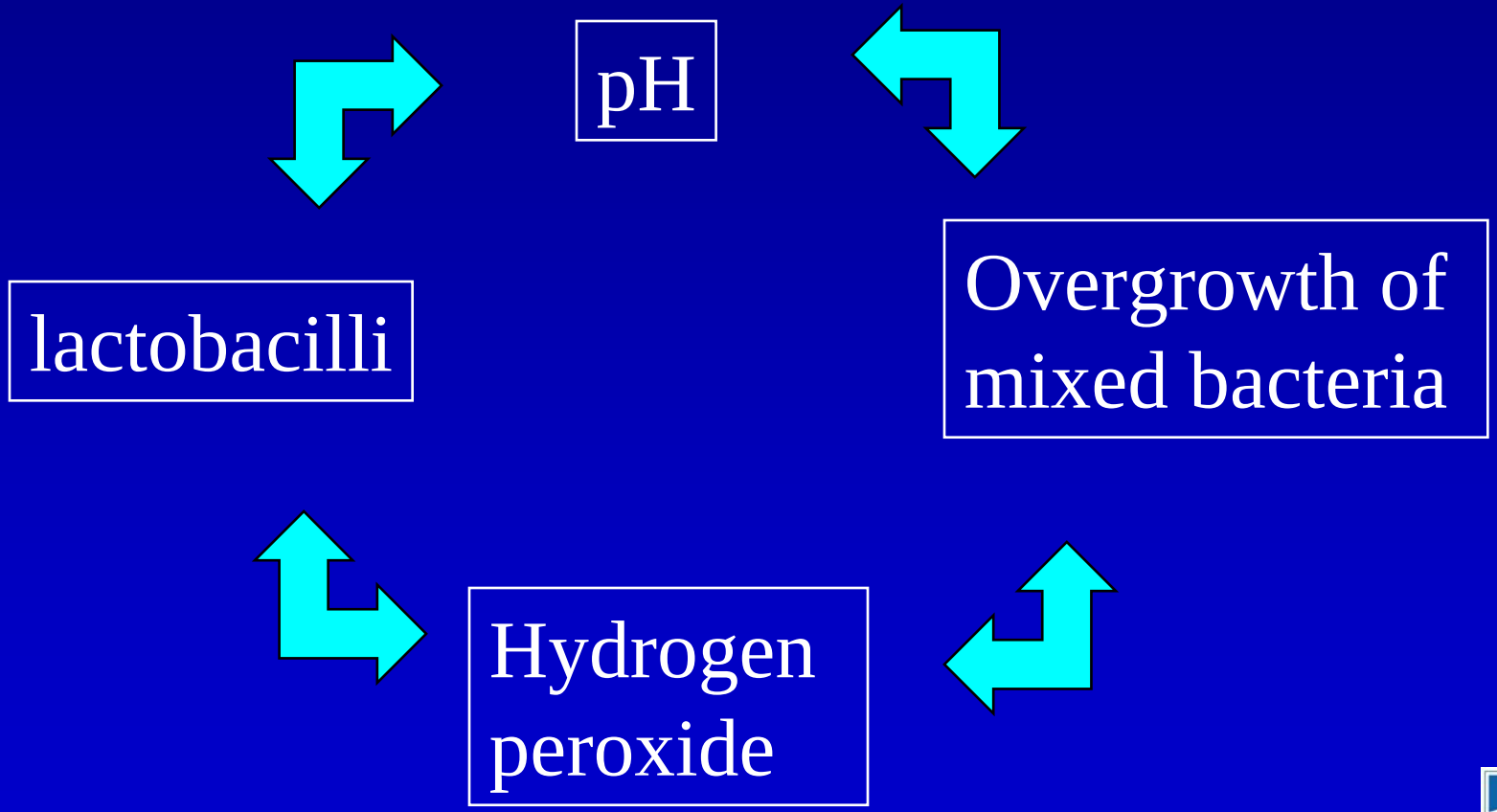
Interplay of Factors Associated with BV



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BV: Adverse Outcomes

- Association with upper tract infection
- Perinatal complications
- Increases HIV transmission
- May increase STD transmission

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BV: Diagnosis

- Amsel criteria (saline wet mount)
- Nugent criteria (Gram stain)
- Point of care tests
  - Affirm VP III™ (BectonDickinson, mod. complexity)
  - FemExam™ (CooperSurgical, waived)
  - OSOM BVBlue™ (Genzyme, waived)
  - QuickVue Pip Activity TestCard™ (Litmus Concepts, mod. complexity)
  - QuickVue pH and amine test™ (Litmus Concepts, waived)

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BV: Treatment

Recommended regimens:

- Metronidazole 500 mg PO BID x 7 d
- Metronidazole gel 0.75% 5 g per vagina QD x 5 d
- Clindamycin cream* 2% 5 g per vagina QHS x 7 d

Alternative regimens:

- Clindamycin 300 mg PO BID x 7 d
- Clindamycin ovules 100 mg per vagina QHS x 3 d

- Metronidazole 2 g PO x 1 deleted as a recommended in 2006 CDC STD Tx Guidelines

**oil-based cream, may weaken condoms and diaphragm*

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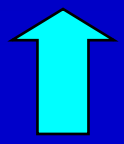
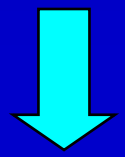
BV: New Treatment

- FDA approved May 2007
- Tinidazole (Tindamax)
  - 1 gm orally once daily for 5 days

  Or
  - 2 gm orally once daily for two days
- Shorter regimen, fewer side effects

 Cost  Adverse effects

Livengood, Obstet Gynecol 2007; 100:302

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BV: Screening and Treatment in Pregnancy

- Studies show conflicting results regarding improvement in poor birth outcomes
- USPSTF Recommendations:
  - "I" rating: "insufficient evidence to recommend for or against routinely screening high-risk pregnant women for BV"
- 2006 CDC Guidelines:
  - "Some specialists recommend screening and oral treatment of women at high risk for pre-term delivery"

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BV: Recurrent Infection

- Up to 85% : recurrence within one year
  - 25% within 4-6 weeks after treatment
- Occurs equally after
  - vaginal or oral therapy
  - metronidazole or clindamycin therapy
- No improvement in recurrence rates after treatment of male partners

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Recurrent BV
Possible Management Strategies

- Use a different recommended regimen
- Vaginal metronidazole gel 0.75% twice weekly*, **
- Avoid douching and intravaginal products
- Condoms to reduce semen exposure
- Replacing lactobacilli?
  - Yogurt and over-the-counter preparations of unproven effectiveness
  - Ongoing research to formulate vaginal lactobacilli replacement preps (*L. crispatis*)

*Sobel JD et al, Am J ObGyn. May 2006 ***2006 CDC Guidelines*

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March 1948

.....and today

Massengill Douche
Beecham, Inc 2001
(GlaxoSmithKline)

www.mum.org

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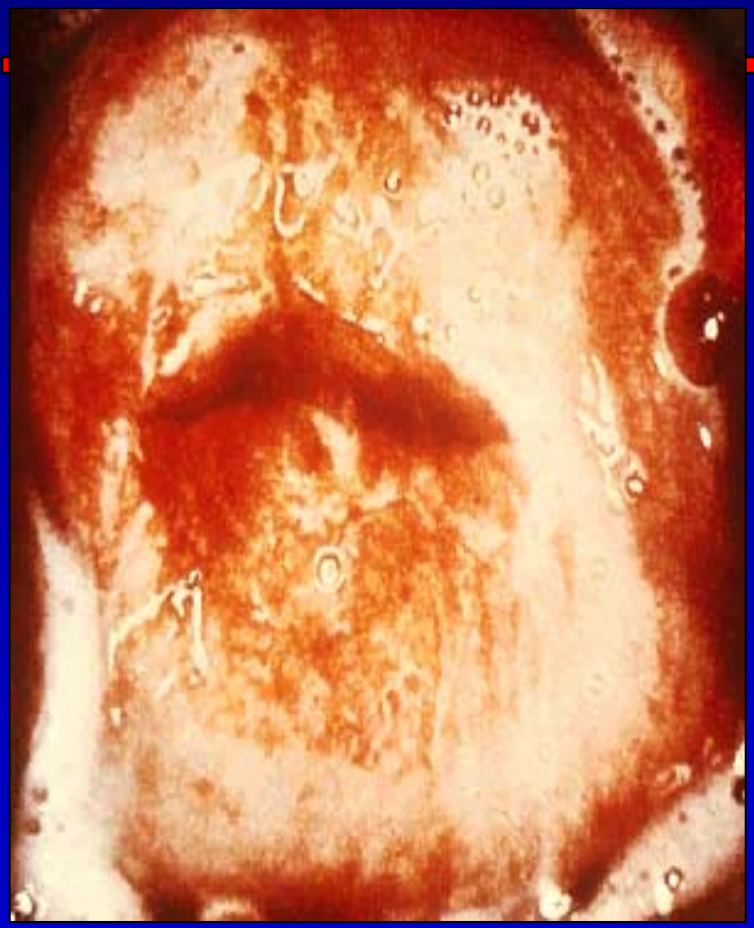
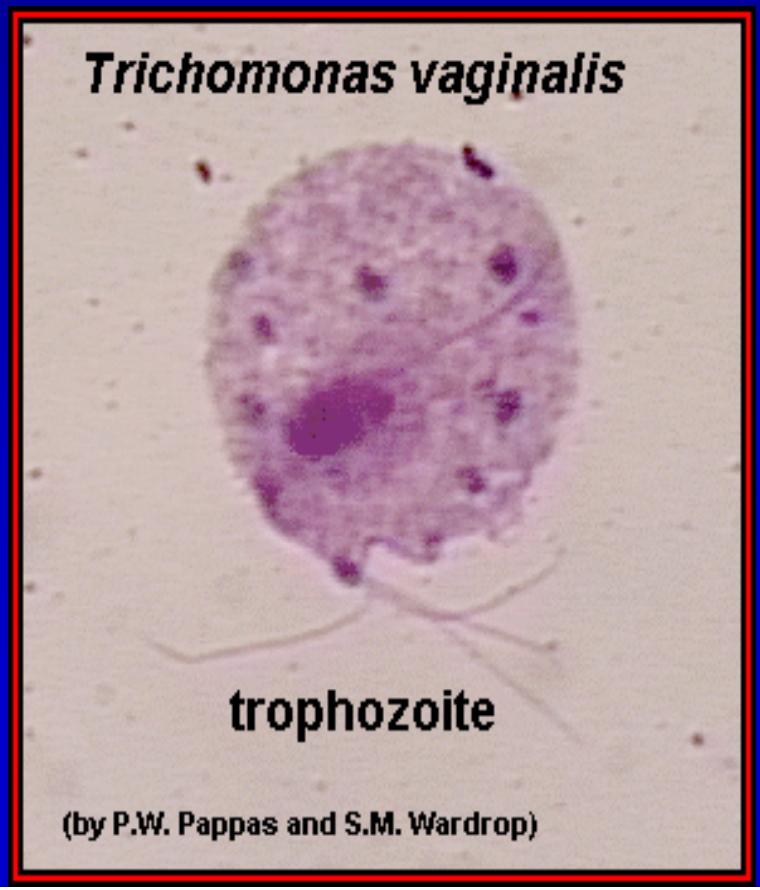
Trichomoniasis



Mosby STD Atlas, 1997



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Trichomoniasis: Treatment

Recommended regimen:

- Metronidazole 2 g PO x 1*
- Tinidazole 2 g PO x 1

Alternative regimen:

- Metronidazole 500 mg PO BID x 7d

Metronidazole highly effective: 95% if both partners treated

**This regimen may be used in pregnancy*

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Evaluation of Possible Resistant Trichomoniasis

- Confirm persistent infection
  - Wet mount
  - POC test
- Consider re-infection
  - Untreated partner
  - New partner
- Obtain isolate and send to CDC for resistance testing and treatment consult

  lab consult:770-488-4115; clinical consult: website: http://www.cdc.gov/std/

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Point-of-Care Tests for *T. vaginalis*

- Affirm VP III™
  (BectonDickinson, mod. complexity)
- OSOM Rapid™ Trichomonas Test
  (Genzyme, waived)
- Xenostrip™ TV
  (Xenotope Diagnostics Inc, waived)
- InPouch™ TV culture
  (BioMed Diagnostics, mod. complexity)

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Treatment Alternatives Resistant Trichomoniasis

- Higher dose metronidazole
  - Metronidazole 500 mg PO BID x 7 days
  - If repeated failure occurs
    - Metronidazole 2 g PO QD x 5 days
- Tinidazole 2 gm PO x 5 days
- Compounded vaginal inserts
  - Paramomycin 250 mg x 7-14 days together with metronidazole orally
  - Furazolidone 100 mg BID x 10-14 days

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Nitroimidazole Allergy

- Hospitalization for oral desensitization
  - Consult a specialist
- Topical treatment with other drugs
  - Paramomycin or furazolidone
  - Cure rates are low

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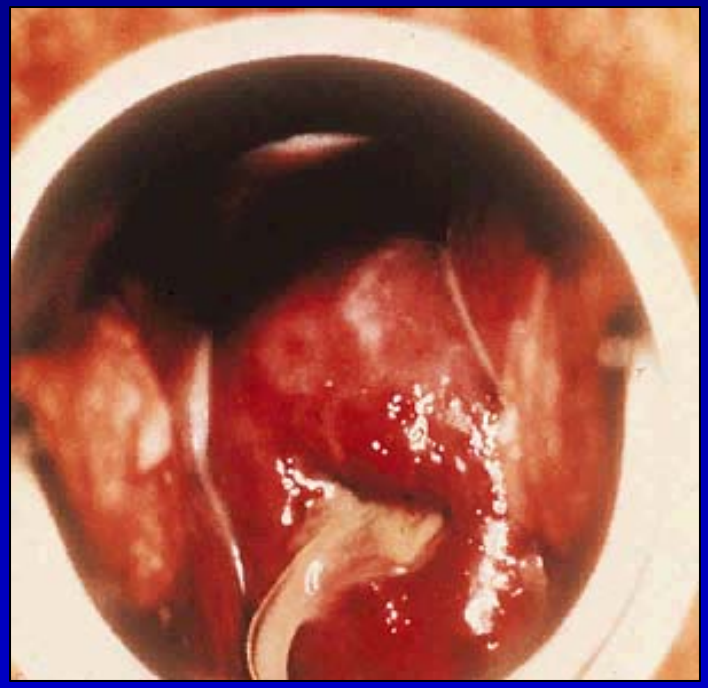
Cervicitis



- Clinically-evident cervical inflammation
- Associations
  - upper tract disease
  - increased HIV shedding
  - poor pregnancy outcomes

Is cervicitis a reliable predictor of CT or GC infection?

Mosby

STD Atlas, 1997

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What causes cervicitis?

- Infectious
  - Chlamydia
  - Gonorrhea
  - Genital herpes
  - Trichomoniasis
  - *Mycoplasma genitalium*
  - Others?
    - Cytomegalovirus
    - Streptococcus species
- Non-infectious
  - Chemical irritants
  - Trauma
  - Abnormal host immune response
  - Persistent disruption of healthy vaginal flora
- Co-infections are common

A significant proportion have no etiology confirmed

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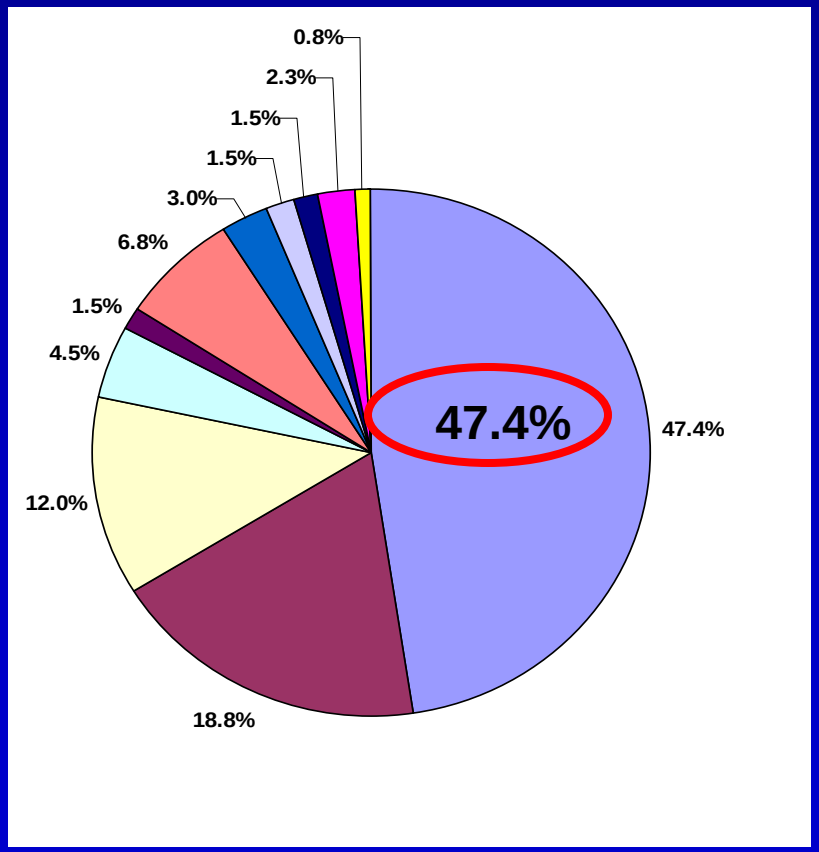
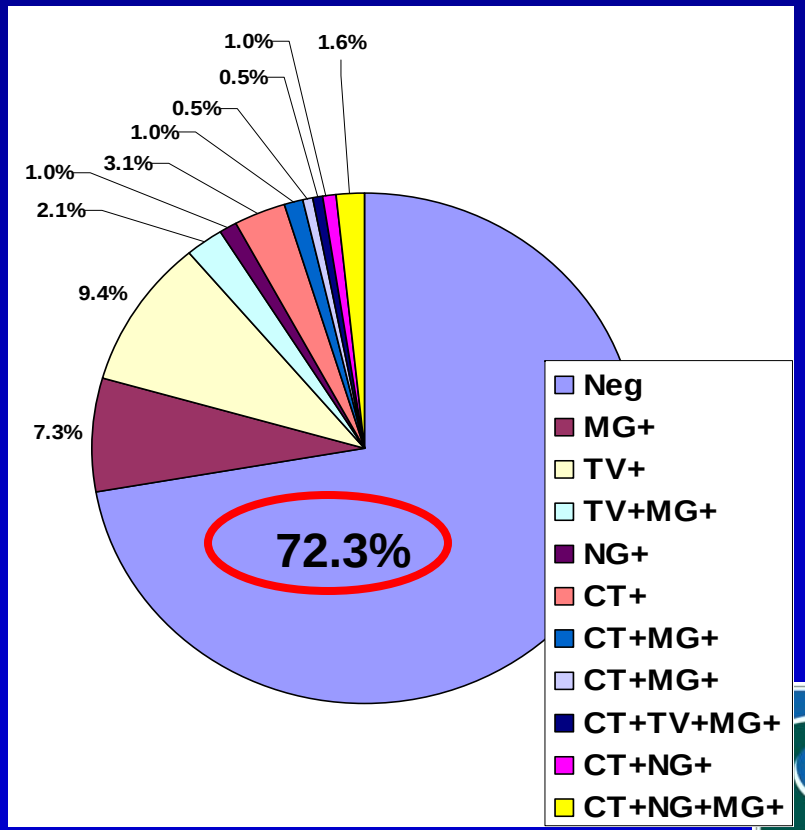
Cervicitis
Single and Co-infections

Coinfection in women with cervicitis



Coinfection in women without cervicitis



Gaydos C, poster, Nat'l STD Prevention Conf, Jacksonville FL, May 2006

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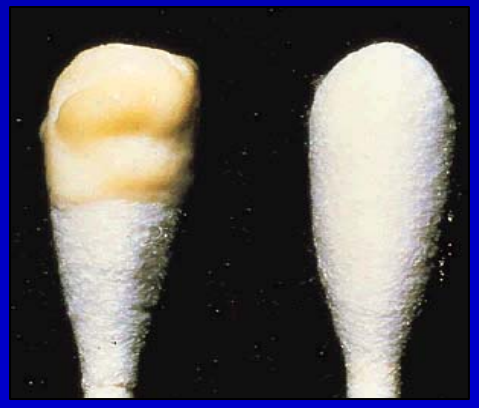
Cervicitis: Diagnosis

Imprecise diagnosis

- Widely-used criteria
  - Mucopurulent endocervical exudate
  - Easily-induced cervical bleeding (friability)
- Other possible diagnostic criteria
  - Erythema
  - Elevated # of WBCs
    - Gram stain
    - Vaginal wet mount

Positive Swab Test



Negative Swab Test

Mosby *STD Atlas, 1997*

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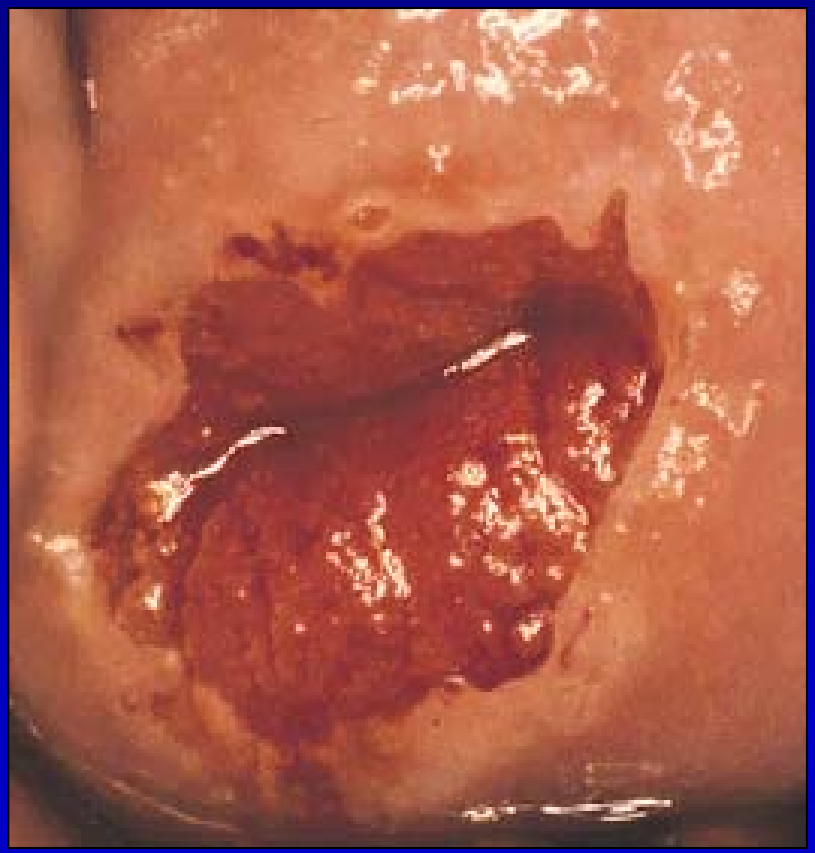
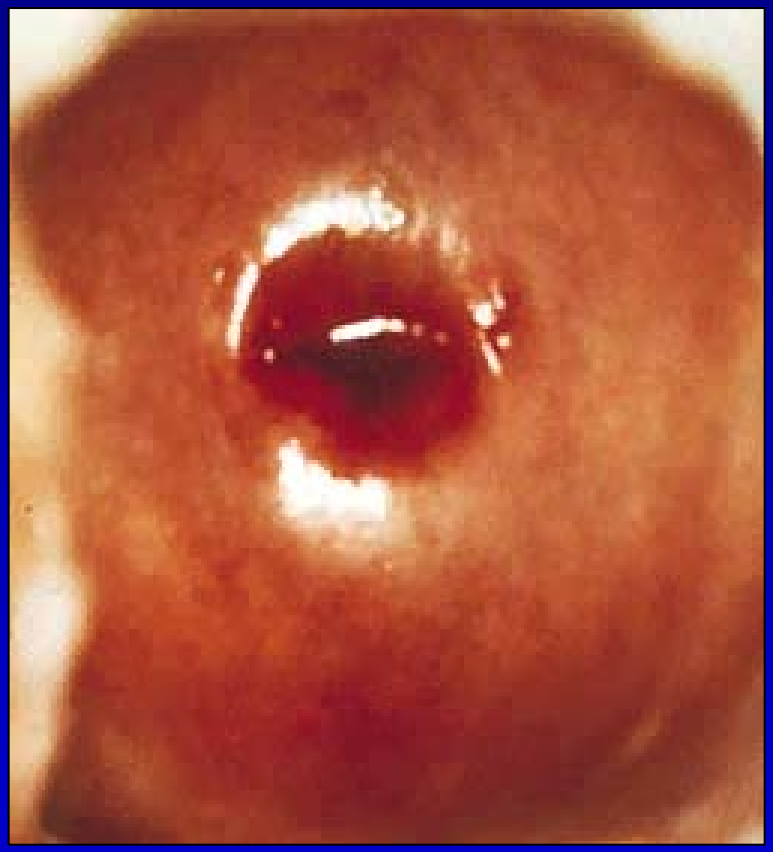
Cervical Ectopy or Erythema?



Ectopy



Minimal ectopy

Mosby *STD Atlas, 1997*

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Cervicitis, Diagnosis Quantifying WBCs

- Wet Mount
  - Varying diagnostic cut-offs
    - 1:1 WBC/epithelial cell
    - 10-30 hpf
    - >30 hpf
- Gram stain is not a widely available test (moderate complexity)

BV
Connection with Cervicitis and PID

- Multiple studies show association of BV with cervicitis, chlamydia infection and/or PID
- Alteration in host defenses (cytokines) may facilitate infection and inflammation

Is cervicitis a sensitive predictor of CT or GC infection?

- Most CT and GC infections do not cause cervicitis
- In most cases of cervicitis, CT and GC tests are negative
- Presence of other predictors will increase PPV

Cervicitis
Deciding Whether to Treat

- Treat for CT if:
  - Age 25 or younger
  - STD risk: new/multiple partners, unprotected sex
  - Follow-up unlikely
- Treat for GC if local prevalence is high (>5%)
- Treat BV if present
- Lower-risk women?
  - Can try 1 course of antibiotics
  - Choice of antibiotic unclear
- Persistent cervicitis, esp. in the absence of identified infection?

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Pelvic Pain Differential Diagnosis

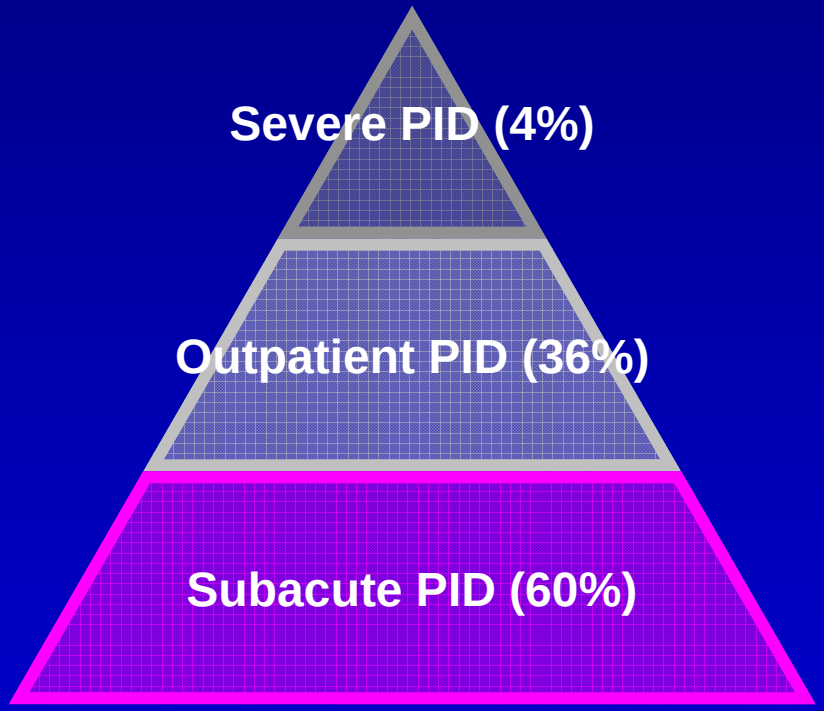
- Gynecologic
  - Ectopic pregnancy
  - Ovarian cyst: rupture, bleeding, torsion
  - Endometriosis
- Gastrointestinal Disease
  - Appendicitis
  - Inflammatory bowel disease
- Urinary tract disorders
  - Renal stones
  - Cystitis

Pelvic Pain: Evaluation

- Clinical history and exam
- β-HCG
  - Pregnancy-related complications
- Ultrasound
  - Pelvic mass/cyst
- Vaginal wet mount
  - PMNs (greater than epithelial cells)
- Urinalysis and culture

Pelvic Inflammatory Disease (PID)

- Ascending infection starting from cervix
- Can involve the endometrium, fallopian tubes, and pelvic peritoneum
- Cervical infection not always present at the time of diagnosis



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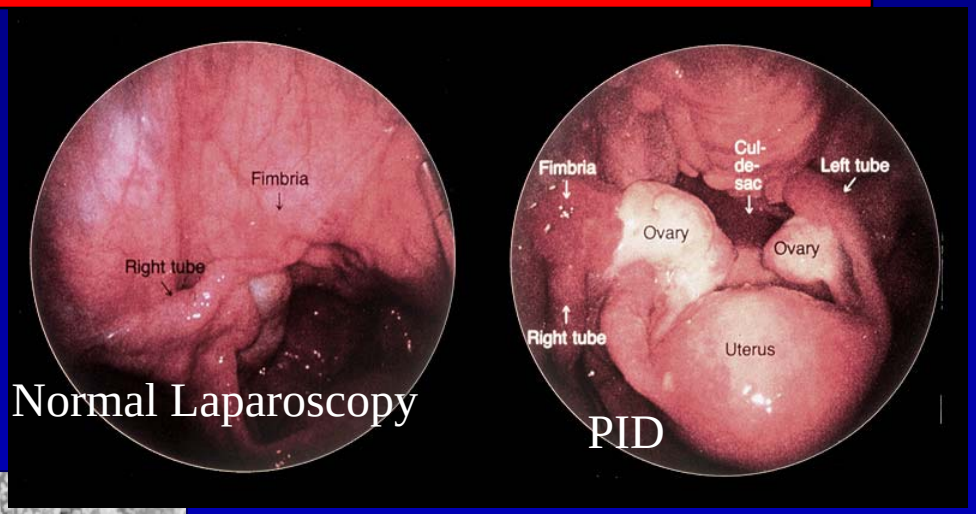
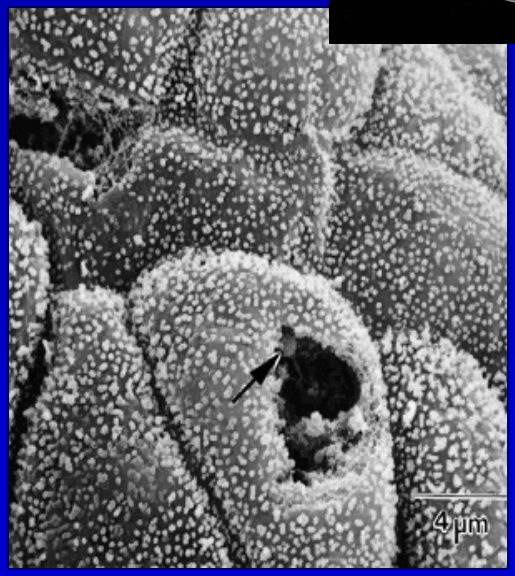
PID: Etiology

- STD associated
  - *C. trachomatis*
  - *N. gonorrhoeae*
  - *Mycoplasma genitalium*
- Non-STD associated (i.e. BV flora)
  - Aerobic (GPC, GNR)
  - Anaerobic (GPC, GNR)

PID: Pathology

GC attaching to microvilli





Cell ruptured by CT

Mosby *STD Atlas, 1997*

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PID Sequelae

- Acute
  - Tubo-ovarian abscess: 3-16%
- Chronic
  - Tubal factor infertility
    - 1 episode = 10%
    - 2 episodes = 20%
    - 3 episodes = 50%
  - Ectopic pregnancy: 7-fold increased risk
  - Chronic pelvic pain: 15-30%

PID: Prevention

- Screening for chlamydia prevents PID
- Role of BV diagnosis and treatment?
- Behavioral interventions
  - Condoms

PID
Diagnostic Challenges

- No single historical, physical or laboratory diagnostic test both sensitive and specific
- Clinical diagnosis has PPV of only 65-90%
  - Highest in young, sexually active women
  - Areas of high prevalence of disease
- Symptoms vary
  - Pelvic pain or pressure
  - Abnormal/post-coital bleeding
  - Dyspareunia

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PID Minimum Clinical Criteria

- **Uterine tenderness**
  OR
- **Adnexal tenderness**
  OR
- **Cervical motion tenderness**

Err on the side of over-treatment,

given the high incidence of adverse outcomes.

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PID: Oral Treatment Regimens

Recommended regimens:

- Ceftriaxone 250 mg IM x 1 ***or***
- Cefoxitin 2 g IM ***with*** probenecid 1 g PO x 1 ***or***
- Other parenteral 3rd generation cephalosporin

PLUS

- Doxycycline 100 mg PO BID x 14 d

WITH OR WITHOUT

- Metronidazole 500 mg PO BID x 14 d

CDC Guidelines Updated April 2007

With or Without Metronidazole???

- BV associated with PID and other upper tract abnormalities
- Assess for BV
  - Wet mount or POC; use metronidazole if BV present
  - If no lab confirmation available, use metronidazole

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Alternate Oral Regimens

- Fluoroquinolones
  - Always use NAAT for GC
  - If GC is confirmed:
    - Retest with culture and get sensitivity
    - Change to non-FQ regimen
- Azithromycin
  - Monotherapy
  - Combo therapy
- Doxycycline and metronidazole

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CDC Indications for Hospitalization

- Surgical emergency cannot be excluded
- Tubo-ovarian abscess
- Pregnancy
- Severe illness (nausea, vomiting, high fever)
- Unable to follow or tolerate outpatient regimen
- Failure to respond to outpatient therapy

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Is outpatient therapy as effective as inpatient?

Evidence from the PEACH *Trial

- Randomized controlled trial, 1996-1999
  - 831 women with mild to moderate PID
  - Inpatient (cefoxitin IV) plus doxycycline PO vs.
  - Outpatient (Cefoxitin IM) plus doxycycline PO
  - Outcomes (mean follow-up 35 months)
    - Acute response to therapy: no difference
    - Chronic sequelae: no difference

*PID Evaluation and Clinical Health study

Ness RB, et al. Obstet Gynecol 2001;186:929-37

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Newer Evidence from the PEACH Trial, 2005

- 49 additional mo of f/u: better power
- Confirmed previous findings: Mild to mod PID: no difference
- Questions regarding severe cases remain
  - These women (criteria to hospitalize) not included in PEACH sample
  - 10% PEACH group with highest temp,/WBC/ pelvic tenderness score: no difference

Ness RB, et al. Obstet Gynecol 2005;106:573-80

PID: Parenteral Regimens

Parenteral regimen A:

Continued for 24 hours after clinical improvement,

- Cefotetan 2 g IV q12h ***or*** Cefoxitin 2 g IV q6h ***plus***
- Doxycycline 100 mg IV or PO q12h
- **Then** Doxycycline 100 mg PO BID for total of 14 d

Parenteral regimen B:

- Clindamycin 900 mg IV q8h ***plus***
- Gentamicin loading dose (2 mg/kg) IV or IM followed by maintenance dose (1.5 mg/kg q8h)
- **Then** Doxycycline 100 mg PO BID ***or***
  Clindamycin 450 mg PO QID for total of 14 d

CDC Guidelines Updated April 2007

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Management of Sex Partners

- Important to prevent re-infection
- Examine and treat partners from last 60 days
  - Test for gonorrhea and chlamydia
  - Treatment (empiric)
    - Broad spectrum
      - Cefixime 400 mg PO **OR** ceftriaxone 125 mg IM **AND**
      - Azithromycin 1 gm PO **OR** doxycycline 100 mg PO bid X 7 days

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PID
Special Circumstances

HIV co-infection

- Similar response to recommended therapies
- Increased risk of tubo-ovarian abscess and pyosalpinx

Pregnancy

- Hospitalize for parenteral treatment

Patients with IUDs

- No evidence supports need for removal
- Careful follow-up

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Key Points

- Use new treatment approaches to recurrent vaginitis
- Consider new diagnostics and co-predictors of infections to help determine who to treat cervicitis
- Screening for CT prevents PID
- Avoid FQs for treatment of PID